Comorbidities are associated with poorer quality of life, functioning and worse symptoms in the 5 years following colorectal cancer surgery: Results from the ColoREctal Wellbeing (CREW) cohort study

Running title: Comorbidities influence wellbeing 5 years after colorectal cancer

Amanda Cummings[1], Chloe Grimmett[1], Lynn Calman[1], Mubarak Patel[1], Natalia Vadimovna Permyakova[1,2], Jane Winter[1,3], Jessica Corner[4], Amy Din[1], Deborah Fenlon[5], Alison Richardson[3,6], Peter W Smith[2], Members of CREW Study Advisory Committee*, Claire Foster[1]

1 Macmillan Survivorship Research Group, Faculty of Health Sciences, University of Southampton, Southampton, UK

2 Social Statistics and Demography, Social Sciences, University of Southampton, Southampton, UK

3 University Hospital Southampton NHS Foundation Trust, Southampton, UK

4 Executive Office, University of Nottingham, Nottingham, UK

5 College of Health and Human Sciences, Swansea University, Swansea, UK

6 Faculty of Health Sciences, University of Southampton, Southampton, UK

* Members listed in Acknowledgements

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ABSTRACT

Objective

More people are living with the consequences of cancer and comorbidity. We describe frequencies of comorbidities in a colorectal cancer cohort and associations with health and wellbeing outcomes up to five years following surgery.

Methods

Prospective cohort study of 872 colorectal cancer patients recruited 2010-2012 from 29 UK centres, awaiting curative intent surgery. Questionnaires administered at baseline (pre-surgery), 3, 9, 15, 24 months, and annually up to 5 years. Comorbidities (and whether they limit activities) were self-reported by participants from 3 months. The EORTC QLQ-C30 and QLQ-CR29 assessed global health/quality of life (QoL), symptoms and functioning. Longitudinal analyses investigated associations between comorbidities and health and wellbeing outcomes.

Results

At baseline, the mean age of participants was 68 years, with 60% male and 65% colon cancer. 32% had one and 40% had $\geq$2 comorbidities. The most common comorbidities were high blood pressure (43%), arthritis/rheumatism (32%) and anxiety/depression (18%). Of those with comorbidities, 37% reported at least one that limited their daily activities. Reporting any limiting comorbidities was associated with poorer global health/QoL, worse symptoms and poorer functioning on all domains over 5 years' follow-up. Controlling for the most common individual comorbidities, depression/anxiety had the greatest deleterious effect on outcomes.

Conclusions

Clinical assessment should prioritise patient-reported comorbidities and whether these comorbidities limit daily activities, as important determinants of recovery of QoL, symptoms and functioning following colorectal cancer. Targeted interventions and support services, including

multi-professional management and tailored assessment and follow-up, may aid recovery of health and wellbeing recovery in these individuals.

Key words: Cancer, Oncology, Colorectal cancer, Comorbidities, Health and wellbeing, Longitudinal, Quality of life, Survivorship

BACKGROUND

Colorectal cancer (CRC) is one of the most common cancers worldwide, with an estimated incidence of over 1.3 million and this is increasing[1]. Five-year survival rates in the UK stand at 57% and 65% in the US[2,3]. CRC is more likely in older adults, with 60% of survivors aged over 65 years[4].

Comorbidity is defined as the presence of distinct medical condition(s) in addition to the particular index disease, in this case CRC[5]. Multiple comorbidity is progressively more common with age, thus older CRC survivors generally present with high levels of comorbidity[6]. CRC survivors also have higher rates of comorbid disease compared with the general population[7], with around 40-50% of CRC patients reported to have $\geq$2 comorbidities[8,9].

Living with comorbidity after CRC diagnosis is now the norm rather than the exception. Therefore, investigation into how comorbidities affect CRC survivors' health and wellbeing has become increasingly important. Cancer survivors often report poorer health and wellbeing compared to healthy populations, and independently, long-term chronic conditions negatively influence QoL[10,11].

Whilst there is a growing body of literature exploring the effect of comorbidities in people recovering from CRC, there is significant variability in study sample sizes[12,13], participant characteristics[14,15], time points of assessment[9,12], and it is not always possible to identify CRC specific data in cohort studies that include multiple tumour groups[16]. In addition, investigations of the impact of comorbidities on QoL, symptoms and functioning following a CRC diagnosis is limited by

cross-sectional design[9,17], a narrow range of outcomes[17,18] and methods used to determine comorbidity status[17,19].

Most studies focus on *number* of comorbidities[9,20], or comorbidity *severity* using weighted scales, where severity is based on the pre-defined mortality risk of individual conditions, such as the Charlson Comorbidity Index (CCI)[13,19,21] or similar indices[22]. Few studies describe patient-reported severity, such as limitations on activities caused by comorbidities. Those that do are either cross-sectional, limited to self-reported depression, do not exclusively examine the impact of comorbidity limitation on wellbeing, or present data from mixed tumour groups[12,19,23].

Few studies have described associations between comorbidities, and health and wellbeing over time. Associations with pain, fatigue and mental wellbeing up to 1 year following a CRC diagnosis, and fatigue and QoL over time in longer term survivors have been described, yet only in relation to the number of comorbidities[18,24]. The role of individual comorbid conditions is largely overlooked in studies.

Only one longitudinal study has mapped comorbidity prevalence up to one year; however, this study was non-population based and limited to CRC survivors >65 years[14]. Similarly, no studies describe the demographic, clinical and treatment characteristics of CRC survivors with comorbidities. Using results from the ColoREctal Wellbeing study (CREW)[25]; a longitudinal cohort study investigating recovery of health and wellbeing in the 5 years following colorectal cancer, this paper aims to determine:

1) The frequency of comorbidities, their limiting effects on daily activities, and the frequency of individual comorbid conditions among CRC survivors.
2) The association between comorbidities, and recovery of QoL, symptom and functioning outcomes.
3) The demographic and clinical factors that characterise comorbid CRC survivors.

METHODS

Design

CREW is a prospective longitudinal cohort study of patients with non-metastatic CRC undergoing curative intent surgery. Further details are described elsewhere[25].

Participants

Eligible patients had a diagnosis of Dukes' stage A-C colorectal cancer, were being treated with curative intent surgery, aged ≥18 years and able to complete questionnaires. Having a prior cancer diagnosis was an exclusion criterion.

Procedure

Participants were recruited from 29 UK hospitals between November 2010 and March 2012. Self-report questionnaires were completed before surgery (baseline) and mailed questionnaires were sent at regular intervals: 3, 9, 15, 24 months, and annually up to 5 years. Clinical and treatment characteristics were identified from NHS medical data. Ethical approval was granted by the UK NHS Health Research Authority NRES Committee South Central - Oxford B (REC ref: 10/H0605/31).

Measures

Full details of the measures used in CREW have been published[25]. Measures that pertain to the findings presented in this paper are summarised below.

Socio-demographic, Clinical and Treatment Data

Clinical and treatment data were obtained (with consent) from medical notes: tumour site, Dukes' stage, nodal involvement, how CRC was detected, family history of CRC, presence of a stoma, neo-adjuvant and adjuvant treatment. Neighbourhood deprivation was derived from postcodes using the Index of Multiple Deprivation[26]. Domestic and employment status were assessed by participant self-report in questionnaires.

Comorbidity Data

Patient self-reported comorbidity status remains an accurate method for health research against clinical record review[27]. Self-reported comorbidity data were collected at 3, 15, 24, 36, 48 and 60 months. The list relating to 12 individual conditions or disease groups was a study specific measure (not formally validated) informed by Ramsey et al[12], with format informed by the Self-Administered Comorbidity Questionnaire[28]. The list (Figure 1) asks whether a doctor has ever told the participant they have the condition, whether the condition limits typical daily activities and the severity of such impact (ranked from 1-7 on Likert scale). At 24 months, an additional question asked whether each condition had been diagnosed before or after CRC diagnosis.

****Insert Figure 1****

QoL, Symptoms and Functioning

QoL, symptoms and functioning were assessed using the validated European Organisation for Research and Treatment of Cancer QoL (EORTC QLQ) core (C30) questionnaire[29] and the CRC component (CR29)[30], from 3 months onwards.

Global health status/QoL scale of the QLQ-C30 was used to represent overall QoL (comprises 2 items). Analyses of symptoms focussed on those most frequently reported in CRC[9,13,31]: pain, fatigue (from QLQ-C30), urinary and bowel symptoms (from QLQ-CR29). Physical, role, cognitive, emotional and social functioning was assessed using QLQ-C30 subscales.

Statistical Analysis

Subscale scores from the EORTC questionnaires were calculated according to published guidelines[29]. To avoid problems with multiple testing of a large number of individual symptoms, summary scores representing urinary symptoms and bowel symptoms were calculated by taking the mean of QLQ-CR29 subscales: (a) urinary frequency, urinary incontinence and dysuria for urinary symptoms, and

(b) blood and mucus in stool, stool frequency, abdominal pain, pain in buttocks/anal area/rectum, bloating, flatulence and faecal incontinence for bowel symptoms.

Due to initial analyses indicating the stability in prevalence and chronicity of comorbidities over follow-up, statistical analyses used 3 month comorbidity data.

In the first part of the analyses, associations between the number of comorbidities reported at 3 months and baseline socio-demographic, clinical and treatment factors, were assessed using the chi-square test or chi-square test for trend, where appropriate. The Index of Multiple Deprivation was categorised into quintiles[26]. Performance status was not captured.

For the second part, longitudinal analyses were conducted using generalised estimating equations, based on all available completed questionnaires up to 60 months. Analyses assessed the associations between EORTC subscale scores as dependent variables and comorbidities reported at 3 months (five most prevalent comorbid conditions, and the comorbidity status itself categorised as none, non-limiting or limiting) as independent variables at the 5% significance level. Separate models were fitted for each EORTC subscale of global health status/QoL, symptoms and functioning.

The first set of multivariable regression models included independent variables separately in each model and were adjusted for time since surgery and those demographic, clinical or treatment factors significantly associated with total numbers of comorbidities in the first analyses.

The second set of multivariable regression models focused on examining multiple effects of the significant comorbidity predictors. Independent (comorbidity) variables statistically significant in the first set of regression models were put together in the second set, again adjusting for time since surgery and demographic/clinical/treatment factors identified as significant in initial analyses.

Participants with missing questionnaires were included in analyses for time-points for which they provided data; there was no imputation of missing questionnaires, or socio-demographic, clinical,

treatment or comorbidity data. Missing data on the EORTC measures were dealt with using published guidelines[29 30].

Longitudinal analyses involving individual comorbidities encompassed the five most prevalent individual conditions (small numbers restricted detailed analysis for less prevalent comorbidities and any associations of individual conditions that limited daily activities).

In line with published guidance, clinically meaningful differences were determined by a >10 point difference in EORTC subscale scores[32].

RESULTS

Participants

1,350 eligible individuals were identified. Of those eligible, 78% (n=1,055) agreed to participate; of whom 86% (n=909) gave full consent to participate and 14% (n=146) gave permission for only clinical data to be collected. 37 were found to be ineligible following surgery. Excluding 11 individuals who withdrew or died between consent and baseline, 861 participants consented to follow-up. This sample is representative of eligible patients treated during the recruitment period. Response rates were 88% at baseline and 69% at 60 months. Comorbidity data were available for 99% of those responding (n=659) at 3 months and 87% (n=324) at 60 months.

Mean age at baseline was 68 years (range 27 to 95 years). The majority were of white ethnic origin and 60% were male. Most participants were retired (60%), and over 60% were married or living with a partner. Most participants had colon cancer (65%), 35% rectal tumours. Over 53% had Dukes' stage B, 20% had stage C1, and 12-14% had stage A or C2 (1% was undetermined) 18% received neo-adjuvant treatment and 46% adjuvant chemotherapy or radiotherapy.

Frequency and Impact of Comorbidities

At 3 months, 28% reported no comorbidities, 32% reported one, 23% two and 17% three or more. Of the 72% (n=476) with comorbidities, the median number was two. Of those with comorbidities,

37% reported at least one that limited their daily activities, with 13% reporting two or more limiting comorbidities (Table 1). The proportion of limiting comorbidities remained consistent over time. Most participants (62% at 3 months) reported that their comorbidities limited daily activities "moderately", which remained fairly consistent over follow-up (Appendix 1).

Individual Comorbidities

The most common individual comorbidities reported at 3 months were high blood pressure (43%), arthritis/rheumatism (arthritis) (32%), depression/anxiety (18%), diabetes/high blood sugar (diabetes) (16%) and asthma/chronic lung disease (lung disease) (16%). There was less than a 7% change in the prevalence of all conditions over follow-up (Appendix 2).

Results suggest that the majority of comorbid conditions were diagnosed prior to CRC diagnosis (participants responded to this question at 24 months). The exceptions to this were stroke/brain haemorrhage and liver disease/cirrhosis, of which 50% and 80% (respectively) were diagnosed following CRC diagnosis. Of note is the relatively high percentage (46%) of comorbid depression/anxiety diagnosed post CRC diagnosis, although numbers were small for analysis. All other conditions (apart from inflammatory bowel disease) were diagnosed before CRC diagnosis in >78% of individuals.

Arthritis and heart failure were reported to be the most limiting conditions. Of participants reporting these conditions, >50% stated it limited their daily activities. Stroke/brain haemorrhage, myocardial infarction and angina were reported as limiting by ≥40% of respondents with each condition, and >35% of participants with depression/anxiety and lung disease reported them as limiting. High blood pressure was the most prevalent, but least limiting condition. Of participants with diabetes, 14% reported the condition as limiting (Appendix 2).

Demographic and Clinical Characteristics

Socio-demographic, clinical and treatment characteristics of CRC patients, and their associations with total number of comorbidities are presented in Appendix 3. Ethnicity is not presented as numbers in minority groups were too small for analysis. Comorbidities were significantly more common in older, retired or unemployed respondents. No significant associations were found between total number of comorbidities and any other socio-demographic, clinical or treatment factors, nor for number of comorbidities that limited daily activities.

Comorbidities and QoL, Symptom and Functioning Outcomes

Due to high correlation between age and employment status, only age at baseline was included in the multivariable regression analyses.

The first set of longitudinal multivariable regression models adjusted for age and time since surgery (from baseline to 60 months), illustrates that the presence of any limiting comorbidities was significantly associated with poorer global health status/QoL, symptom and functioning outcomes across all domains ($p<0.001$), including: increased fatigue, pain, urinary and bowel symptoms, and reduced physical, role, emotional, cognitive and social functioning (Appendix 4). Findings illustrated clinically meaningful differences associated with the presence of limiting comorbidities across all outcomes (except for urinary and bowel symptoms). In contrast, the presence of non-limiting comorbidities was only significantly associated with increased pain and worse physical functioning ($p<0.05$).

Of the five most prevalent individual comorbid conditions reported at 3 months, arthritis and depression/anxiety were significantly associated with poorer global health status/QoL, symptom and functioning outcomes across all domains ($p<0.001$). Depression/anxiety appeared to have the greatest association with poorer outcomes, with clinically meaningful differences across all outcomes (except for urinary and bowel symptoms). Lung disease was also significantly associated

with poorer outcomes, with the exception of urinary symptoms. Diabetes and high blood pressure were significantly associated with increased pain and poorer physical functioning, with diabetes also associated with worse urinary symptoms (Appendix 4).

Once adjusted for all significant comorbidity predictors, final multivariable regression models confirmed that the presence of any limiting comorbidities remained a statistically strong and significant predictor of all health and wellbeing outcomes ($p<0.001$), with the exception of emotional functioning (Table 2). The biggest and clinically significant differences were observed for pain, fatigue, physical, role, social and cognitive functioning.

The presence of depression/anxiety remained a statistically significant and strong predictor of poorer outcomes across all domains, with the exception of urinary symptoms. Clinically meaningful differences were observed for global health status/QoL, fatigue, emotional and social functioning. Arthritis, diabetes and high blood pressure did not remain significantly associated with any outcomes. Lung disease remained statistically significant only in association with poorer global health status/QoL and physical functioning ($p<0.05$).

For participants reporting both limiting comorbidities and depression/anxiety, differences in outcome scores were approximately doubled for domains including fatigue, pain, physical, role and social functioning, with highly clinically significant differences in outcome scores of >20.

DISCUSSION

This is the first paper to describe the stability of comorbidity prevalence, individual comorbidities and patient-reported limitations of comorbidities, and demonstrate their significant associations with poorer QoL, symptoms and functioning up to 5 years following CRC diagnosis. We demonstrate that it is not the presence of comorbidities per se, but the limitations on daily activities imposed by comorbidities, which has the greatest impact on health and wellbeing.

Frequency and prevalence of comorbidity

Our results demonstrate that 27% of CRC survivors (37% of those with comorbidities), report at least one comorbidity that limits their daily activities. Ramsey et al, the only other study to investigate self-reported comorbidity limitation, found similar findings, with 32% reporting currently limiting comorbidities, although their findings relate to longer-term (> 5 years) CRC survivors[12]. Our results also add to growing evidence that 70-80% of CRC survivors are living with at least one comorbidity[9,12,18].

Anxiety and depression are increasingly recognised as common following CRC[17], yet CREW adds to only a handful of studies to include them in its assessment of comorbidity[8,18]. Approximately half of individuals stated their depression/anxiety was not pre-existing, but was diagnosed after CRC. Despite low response rates for this question (50%), high rates of depression post-cancer diagnosis, particularly in CRC, have been demonstrated elsewhere[33]. The stability in prevalence of depression/anxiety in the 5 year follow-up reported here, suggests that often, diagnoses may occur within 3 months of a CRC diagnosis. Our findings highlight the importance of screening for mental wellbeing and offering appropriate support. This is emphasised by research detailing how significantly fewer CRC survivors actively seek help for psychological problems than for physical concerns[34].

The frequency of hypertension, arthritis, diabetes and lung disease are comparable to other studies[7,18], and reflect their prevalence in the general population[35]. Results demonstrating a $\leq$10% prevalence of angina, myocardial infarction and heart failure in the CREW cohort, are at odds with higher prevalence in other CRC studies, and in the general population[8,34]. This likely reflects differences in the criteria for assessing conditions, for example as collective 'heart disease' or here, as separate conditions.

Association of comorbidities with QoL, functioning and symptom outcomes

Our data confirm the importance of understanding whether comorbidities are disrupting daily activities, as these can have a greater, negative impact on health and wellbeing during recovery from CRC. Even after accounting for all significant comorbidity predictors, patient-reported limitations of comorbidities prevailed as a strong and significant predictor across all QoL, functioning and symptom outcomes. The only exception to this was emotional functioning, where the presence of depression/anxiety held prominent significance. Astrup et al also described associations between limitations of comorbidities and reduced QoL and greater symptom experience, although their study was not limited to CRC[23]. The only other study to describe similar associations with QoL in CRC patients, combined patient reported and pre-defined severity scores, meaning that results do not solely reflect patient reports of limitation[12]. Studies using clinically derived assessments (pre-defined weighted scales) of comorbidity severity, have been inconsistent in demonstrating a link between greater severity and poorer QoL[19,22]. Weighted severity scores were designed to predict survival outcomes and therefore do not capture the complexity and impact of living with comorbidities[21]. Research demonstrating associations between performance status of cancer patients and QoL outcomes, supports limitation of daily activities as an important influencer of health and wellbeing[16]. Our findings demonstrate that self-reported limitations of comorbidities have an important and much greater influence on health and wellbeing outcomes, compared to comorbidity presence alone. Whilst the presence and clinically defined severity of comorbidities are important, future assessment should include appraisal of how much they disrupt people's lives.

Perhaps unsurprisingly, the strongest effects of having a limiting comorbidity were seen with pain, physical and role functioning outcomes. Identified associations with pain are supported elsewhere[36,37]. However, we describe for the first time the persistent association between limiting comorbidities and symptom outcomes up to 5 years post CRC, in particular the association between comorbidities and poorer urinary and bowel symptoms. Similar associations have been described in

rectal cancer[38], but this is a new finding in CRC. These findings hold significance, as multiple studies report urinary and bowel symptoms as predominant, persistent and burdensome following CRC treatment[9,31].

Previous cross-sectional studies have demonstrated links between depression/anxiety and poorer QoL, fatigue, pain, physical and emotional functioning in CRC survivors[17,19]. Our findings support and expand on this previous literature by demonstrating that depression/anxiety is the most significant individual predictor of poorer health and wellbeing outcomes (with the exception of urinary symptoms) in CRC survivors for up to 5 years, even after adjusting for the presence of any limiting comorbidities and other individual conditions. Moreover, our findings suggest a double health and well-being burden of having both depression/anxiety and any limiting comorbidities.

Interestingly, significant associations of arthritis, as the most limiting comorbidity, disappeared for all outcomes after the inclusion of the presence of any limiting comorbidities in the final models, which likely accounted for the health importance of arthritis. This finding suggests that arthritis, by its limiting nature, is associated with prolonged and poor health and wellbeing outcomes, supporting its associations with greater pain and poorer physical functioning seen elsewhere[8].

Study Limitations

Previous cancer studies have demonstrated that participants are less likely to have severe comorbidities than non-responders[22]. This should be taken into consideration when interpreting results, as it is possible that our findings may under-represent the true extent and impact of comorbidities. Assessment of EORTC QLQ-C30, QLQ-CR29 and comorbidities was not included within questionnaires until 3 months due to burden of data collection close to diagnosis. Participants were asked whether comorbidities were diagnosed prior to their CRC diagnosis at 24 months, as such, responses are liable to recall bias. The list of comorbidities available for self-report

was limited to 12 individual conditions or disease groups and did not encompass all potential comorbid conditions (for example, obesity). A prior diagnosis of cancer was an exclusion criterion, meaning that previous cancer diagnoses could not be included in comorbidity assessment. Falling response rates over follow-up mean that apparent trends in comorbidities over time need to be interpreted with caution. Any apparent decline in absolute numbers of individuals reporting comorbidities could be due to more unwell individuals withdrawing from the study.

Conclusions and Clinical Implications

Our findings highlight the importance of identifying patient-reported presence and limitations of comorbidities, as important health and wellbeing predictors both during and beyond CRC treatment. The stability in prevalence and severity of comorbidity, suggests that CRC patients at risk of poorer outcomes up to 5 years following a diagnosis, can be identified early, and appropriate support put in place. As such, key consideration should be given to optimising comorbidity management before CRC treatment and clinical follow-up that incorporates comorbidity assessment, is individualised, and takes place as soon as possible following a CRC diagnosis.

The International Society of Geriatric Oncology (SIOG) recommends geriatrician involvement in the management of cancer patients with comorbidities, and treatment decisions that consider comorbidities[39]. We propose that targeted interventions and support services, including multi-professional management and tailored assessment and follow-up, may aid recovery of health and wellbeing.

CREW highlights the importance of including conditions such as musculoskeletal and mood disorders, and patient-reported limitations, in future clinical and research assessments of comorbidity. The inclusion of self-reported health status in the assessment of comorbid CRC patients, is a

recommendation echoed by NICE multimorbidity guidance[40] and could help to identify CRC patients at risk of reduced health and wellbeing.

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Table 1. Number of comorbidities and number of limiting comorbidities for the CREW cohort (reported at 3 months following primary CRC surgery)

Number of comorbidities	**3 months n=659**	**Number of limiting comorbidities**	**3 months n=476**
0	183 (27.7%)	0	249 (52.3%)
1	211 (32.0%)	1	115 (24.2%)
2	150 (22.8%)	≥2	62 (13.0%)
≥3	115 (17.4%)	*Missing data*	50 (10.5%)
Presence of any comorbidities	476 (72.2%)	Presence of any limiting comorbidities	177 (37.2%)

Table 2. Mean differences in EORTC subscale scores over follow-up between 3 and 60 months following surgery, estimated from multivariable regression models adjusted for age at baseline, time since surgery, comorbidity status and five most prevalent conditions

Independent Variables	Dependent Variables: EORTC subscale scores [1]									
	Global health status / QoL[2]	Fatigue[3]	Pain[3]	Urinary symptoms[3,4]	Bowel symptoms[3,5]	Physical functioning[2]	Role functioning[2]	Emotional functioning[2]	Cognitive functioning[2]	Social functioning[2]
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9	Model 10
1) Comorbidity status:										
- None (ref)	0	0	0	0	0	0	0	0	0	0
- Yes, non-limiting comorbidities	0.4	0.4	2.8	0.6	1.4	-1.7	0.2	1.3	-0.7	0.6
- Yes, limiting comorbidities	-8.3***	13.6***	19.1***	6.3***	6.4***	-16.3***	-15.0***	-5.1	-10.2***	-11.3***
2) High blood pressure										
- No (ref)			0			0				
- Yes			-1.0			0.01				
3) Arthritis/rheumatism										
- No (ref)	0	0	0	0	0	0	0	0	0	0
- Yes	-3.2	3.3	4.8	0.9	0.9	-0.9	-3.2	-0.9	0.5	-3.6
4) Depression/anxiety										
- No (ref)	0	0	0	0	0	0	0	0	0	0
- Yes	-10.0***	12.6***	6.7*	3.2	4.2*	-8.7**	-9.1**	-18.8***	-9.6**	-10.4***
5) Diabetes/high blood sugar										
- No (ref)			0	0		0				
- Yes			1.6	2.7		-2.2				
6) Asthma/chronic lung disease										
- No (ref)	0	0	0		0	0	0	0	0	0
- Yes	-5.2*	3.0	-0.3		-0.3	-5.0*	-4.5	-1.8	-1.8	0.2
7) age at baseline	-0.1	0.01	-0.2	0.1*	-0.3***	-0.4***	-0.1	0.2*	0.1	0.1
8) time since surgery	0.1***	-0.2***	-0.1**	0.02	-0.1***	0.1**	0.2***	0.1***	0.2***	0.3***

Notes: *** p<0.001; ** p<0.01; * p<0.05; Grey areas indicate that the referred independent variable was not included in the final multivariable model of the referred outcome, because it was statistically insignificant in the original model adjusted only for age and time since surgery (see Appendix 4).

[1] EORTC subscale from QLQ-C30 or CR-29

[2] *Higher* scores for global health status/QoL and functioning subscales indicate *better* health/QoL and functioning

[3] *Higher* scores for symptom subscales indicate *worse* symptoms

[4] Urinary symptoms include urinary frequency, urinary incontinence and dysuria

[5] Bowel symptoms include blood and mucus in stool, stool frequency, abdominal pain, pain in buttocks/anal area/rectum, bloating, flatulence and faecal incontinence

The following questions are about other illnesses that you may have.
For each of the illnesses please answer '**yes**' or '**no**' as to whether your doctor has ever told you that you have the condition and whether any of your current activities are limited by the condition?

	Has a doctor ever told you that you have this condition?			If '**yes**' has the condition limited activities you would do during a typical day? E.g. work, working around the house or garden, bathing or dressing yourself, social activities		If '**yes**' how severely has the condition limited your activities? Please choose a number from 1, which is slightly limited, to 7, which is severely limited.						
	Yes	No	Don't know	Yes	No	Slightly 1	2	3	4	5	6	Severely 7
Arthritis or rheumatism	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Diabetes or high blood sugar	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Inflammatory bowel disease, colitis or Crohn's disease	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bleeding from stomach ulcers	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Asthma, chronic lung disease, bronchitis or emphysema	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Heart failure (condition)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
High blood pressure	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Heart attack or myocardial infarction	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Chest pain or angina	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Liver disease or cirrhosis	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Depression or anxiety	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Figure 1. Self-report comorbidities section of CREW questionnaires

Appendix 1. Number and severity of limiting comorbidities reported at 3, 15, 24, 36, 48 and 60 months following primary colorectal cancer surgery

	How severely has the condition limited your activities n(%)				Total number of limiting comorbidities
	1-2 Mild	3-5 Moderate	6-7 Severe	Missing data	
3 Months	69 (25%)	170 (62%)	27 (10%)	7 (3%)	N = 273
15 Months	64 (31%)	104 (50%)	26 (12%)	15 (7%)	N = 209
24 Months	65 (34%)	101 (52%)	22 (11%)	5 (3%)	N = 193
36 Months	51 (31.7%)	87 (54.0%)	18 (11.2%)	5 (3.1%)	N = 161
48 Months	51 (27.6%)	104 (56.2%)	25 (13.5%)	5 (2.7%)	N = 185
60 Months	34 (22.1%)	94 (61.0%)	20 (13.0%)	6 (3.9%)	N = 154

Appendix 2. Prevalence of individual self-reported comorbidities at 3, 15, 24, 36, 48 and 60 months following primary colorectal cancer surgery, and prevalence of those reported to limit daily activities at 3 months

Self-reported comorbidity	Prevalence of Comorbidity (n= answered question)						
	3 Months		15 Months	24 Months	36 Months	48 Months	60 Months
	Prevalence at 3 months	Prevalence of those with comorbidity that report it limits daily activities	Prevalence at 15 months	Prevalence at 24 months	Prevalence at 36 months	Prevalence at 48 months	Prevalence at 60 months
High blood pressure	259 (43.2%) N = 600	15 (5.8%)	214 (41.2%) N = 519	184 (38.5%) N = 478	140 (38.1%) N = 367	141 (39.8%) N = 354	134 (43.8%) N = 306
Arthritis or rheumatism	186 (32.0%) N = 581	99 (53.2%)	174 (34.2%) N = 509	155 (32.6%) N = 476	133 (36.9%) N = 360	126 (36.6%) N = 344	105 (34.3%) N = 306
Depression or anxiety	100 (18.2%) N = 550	36 (36.0%)	71 (14.4%) N = 494	66 (14.0%) N = 470	46 (13.3%) N = 345	51 (15.4%) N = 332	40 (13.7%) N = 292
Diabetes or high blood sugar	89 (16.2%) N = 547	12 (13.5%)	82 (16.5%) N = 496	74 (15.7%) N = 472	65 (19.0%) N = 342	59 (18.0%) N = 328	66 (23.1%) N = 286
Asthma, chronic lung disease, bronchitis or emphysema	85 (15.7%) N = 542	30 (35.3%)	70 (14.3%) N = 491	66 (13.9%) N = 475	49 (14.2%) N = 345	49 (14.6%) N = 335	48 (16.4%) N = 292
Chest pain or angina	55 (10.2%) N = 540	22 (40.0%)	40 (8.1%) N = 492	43 (9.1%) N = 473	28 (8.3%) N = 339	23 (6.9%) N = 333	24 (8.2%) N = 293
Inflammatory bowel disease, colitis or Crohn's disease	46 (8.7%) N = 527	16 (34.8%)	31 (6.4%) N = 482	27 (5.8%) N = 468	17 (5.0%) N = 340	15 (4.6%) N = 329	15 (5.2%) N = 288
Heart attack or myocardial infarction	40 (7.5%) N = 533	16 (40%)	40 (8.2%) N = 490	36 (7.7%) N = 469	22 (6.6%) N = 332	22 (6.6%) N = 333	20 (6.8%) N = 293
Stroke or brain haemorrhage	21 (4.0%) N =529	9 (42.9%)	11 (2.3%) N = 485	10 (2.2%) N = 465	8 (2.4%) N = 335	11 (3.3%) N = 330	11 (3.8%) N = 289
Heart failure	21 (4.0%) N = 527	11 (52.4%)	25 (5.1%) N = 487	21 (4.5%) N = 468	21 (6.1%) N = 342	18 (5.4%) N = 335	13 (4.5%) N = 290
Liver disease or cirrhosis	8 (1.5%) N = 525	1 (12.5%)	13 (2.7%) N = 485	11 (2.3%) N = 469)	11 (3.3%) N = 338	7 (2.1%) N = 327	5 (1.7%) N = 289
Bleeding from stomach ulcers	3 (0.6%) N = 523	0 (0.0%)	2 (0.4%) N = 487	4 (0.9%) N = 469	0 (0.0%) N = 338	5 (1.5%) N = 329	3 (1.0%) N = 287

Appendix 3. Number of comorbidities reported at 3 months following colorectal cancer surgery according to socio-demographic, clinical and treatment characteristics

		Number of Comorbidities (at 3M)					Presence of comorbidities (≥1)	Chi Square test comparing presence versus absence of comorbidities: p-value
		0	1	2	3+	Total		
Socio-demographic Factors	Age group (years)							< 0.001[t]
	≤50	25 (58%)	10 (23%)	5 (12%)	3 (7%)	43	18 (42%)	
	51-60	32 (35%)	31 (34%)	22 (24%)	7 (8%)	92	60 (65%)	
	61-70	59 (27%)	75 (35%)	48 (22%)	35 (16%)	217	158 (72.8%)	
	71-80	28 (18%)	45 (29%)	43 (28%)	38 (25%)	154	126 (81.8%)	
	>80	8 (16%)	18 (35%)	15 (29%)	10 (20%)	51	43 (84.3%)	
	Gender							0.458
	Male	113 (29%)	133 (34%)	87 (22%)	63 (16%)	396	283 (71.5%)	
	Female	70 (27%)	78 (30%)	63 (24%)	52 (20%)	263	193 (73.4%)	
	Deprivation Index (quintiles)							0.206[t]
	1st (least deprived)	42 (31%)	44 (32%)	32 (23%)	19 (14%)	137	95 (69.3%)	
	2nd	37 (26%)	46 (33%)	35 (25%)	23 (16%)	141	104 (73.8%)	
	3rd	33 (27%)	37 (30%)	30 (25%)	22 (18%)	122	89 (73.0%)	
	4th	33 (28%)	49 (41%)	22 (18%)	16 (13%)	120	87 (72.5%)	
	5th (most deprived)	32 (25%)	32 (25%)	30 (23%)	34 (27%)	128	96 (75.0%)	
	Domestic Status							0.314
	Married/Living with partner	128 (29%)	145 (32%)	106 (24%)	68 (15%)	447	319 (71.4%)	
	Single/Widowed/ Divorced/ Separated	42 (25%)	51 (30%)	39 (23%)	36 (21%)	168	126 (75.0%)	
	Employment Status							< 0.001
	Employed (Employed FT, PT, on unpaid or sick leave)	76 (43%)	60 (34%)	31 (18%)	9 (5%)	176	100 (56.8%)	
	Unemployed (Unemployed or disabled does not work)	4 (2%)	12 (41%)	7 (24%)	6 (21%)	29	25 (86.2%)	
	Retired	89 (22%)	124 (31%)	106 (26%)	88 (22%)	407	318 (78.1%)	
Cli	Tumour site							0.133

	Colon	109 (25%)	138 (32%)	107 (25%)	77 (18%)	431	322 (74.7%)	
	Rectum	74 (33%)	73 (32%)	42 (19%)	38 (17%)	227	153 (67.4%)	
	Dukes' stage							0.307[t]
	Stage A	30 (29.4%)	25 (24.5%)	29 (28.4%)	18 (17.6%)	102	72 (70.6%)	
	Stage B	97 (28%)	117 (34%)	66 (19%)	65 (19%)	345	248 (71.9%)	
	Stage C1	31 (24%)	41 (31%)	38 (29%)	21 (16%)	131	100 (76.3%)	
	Stage C2	22 (31%)	23 (33%)	16 (23%)	9 (13%)	70	48 (68.6%)	
	Nodal Involvement							0.594[t]
	N0	120 (28%)	134 (32%)	88 (21%)	81 (19%)	423	303 (71.6%)	
	N1	29 (23%)	41 (33%)	34 (27%)	20 (16%)	124	95 (76.6%)	
	N2	23 (31%)	25 (34%)	16 (22%)	10 (14 %)	74	51 (68.9%)	
	How cancer was detected							0.671
	Screening	39 (25%)	55 (36%)	36 (23%)	25 (16%)	155	116 (74.8%)	
	Symptomatic	130 (29%)	139 (31%)	104 (23%)	83 (18%)	456	326 (71.5%)	
	Emergency surgery/other	12 (40%)	8 (27%)	5 (17%)	5 (17%)	30	18 (60.0%)	
	Family History (of CRC)							0.235
	Yes	31 (40%)	25 (32%)	13 (17%)	9 (12%)	78	47 (60.3%)	
	No	93 (28%)	111 (34%)	73 (22%)	50 (15%)	327	234 (71.6%)	
Treatment Factors	Presence of a stoma							0.665
	Yes	69 (30%)	73 (32%)	46 (20%)	39 (17%)	227	158 (69.6%)	
	No	113 (27%)	136 (32%)	101 (24%)	74 (18%)	424	311 (73.3%)	
	Neo-adjuvant treatment							0.148
	Yes	37 (31%)	43 (36%)	19 (16%)	20 (17%)	119	82 (68.9%)	
	No	146 (27%)	168 (31%)	128 (24%)	94 (18%)	536	311 (73.3%)	
	Adjuvant treatment							0.538
	Yes	76 (32%)	71 (30%)	59 (25%)	32 (13%)	238	162 (68.1%)	
	No	107 (26%)	140 (33%)	90 (21%)	83 (20%)	420	313 (74.5%)	

[t] Chi² test for trend used for age group, deprivation index, Dukes' stage, nodal involvement

Appendix 4. Mean differences in EORTC subscale scores over follow-up between 3 and 60 months following surgery, estimated from multivariable regression models adjusted for age at baseline and time since surgery

Independent Variables	Dependent Variables: EORTC subscales [1]									
	Global health status / QoL[2]	Fatigue[3]	Pain[3]	Urinary symptoms[3,4]	Bowel symptoms[3,5]	Physical functioning[2]	Role functioning[2]	Emotional functioning[2]	Cognitive functioning[2]	Social functioning[2]
1) Comorbidity status *(ref: none):*										
- Yes, non-limiting comorbidities	-2.0	2.8	3.7*	1.8	1.2	-3.7*	-1.8	-1.0	-1.7	-1.2
- Yes, limiting comorbidities	-14.0***	19.1***	24.3***	7.2***	7.4***	-20.9***	-20.2***	-10.7***	-11.8***	-16.1***
2) High blood pressure *(ref: no)*	-3.1[+]	2.3	4.0**	0.6	-1.1[+]	-4.0**	-2.9[+]	0.1	0.6	-1.6
3) Arthritis/rheumatism *(ref: no)*	-8.6***	10.9***	17***	4.2***	4.9***	-12.4***	-13.2***	-6.8***	-5.6***	-11.6***
4) Depression/anxiety *(ref: no)*	-13.7***	17.6***	15.9***	5.8***	6.7***	-16.8***	-15.6***	-22***	-13.9***	-16.1***
5) Diabetes/high blood sugar *(ref: no)*	-3.6[+]	3.6	5.0*	3.9***	-0.2	-6.1**	-2.5	1.8	1.2	1.4
6) Asthma/chromic lung disease *(ref: no)*	-7.3**	8.7**	7.0**	1.8	2.8*	-11.9***	-9.3***	-4.8*	-5.9**	-5.4**

*** p<0.001; ** p<0.01; * p<0.05

[+] was statistically significant (p<0.05) in a bivariate model and multivariable model adjusted only for time since surgery, but became insignificant after adjusting for age.

[1] EORTC subscale from QLQ-C30 or CR-29

[2] *Higher* scores for global health status/QoL and functioning subscales indicate *better* health/QoL and functioning

[3] *Higher* scores for symptom subscales indicate *worse* symptoms

[4] Urinary symptoms include urinary frequency, urinary incontinence and dysuria

[5] Bowel symptoms include blood and mucus in stool, stool frequency, abdominal pain, pain in buttocks/anal area/rectum, bloating, flatulence and faecal incontinence